ISAC APPLICATION FORM
PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

ISAC use only:	Chair	**IMPORTANT**
Protocol Number	15_107R	**If you have any queries, please contact ISAC Secretariat:** ISAC@cprd.com
Date submitted	20 May 2015	

1. Study Title

What are the effects of varenicline compared with nicotine replacement therapy on long term smoking cessation and clinically important outcomes?

2. Principal Investigator (full name, job title, organisation & e-mail address for correspondence regarding this protocol)

Dr Neil Davies, Research Associate, MRC IEU University of Bristol neil.davies@bristol.ac.uk

3. Affiliation (full address)

Barley House, Oakfield Grove
Bristol, BS8 2BN

4. Protocol's Author (if different from the principal investigator)

5. List of all investigators/collaborators (*please list the names, affiliations and e-mail addresses* of all collaborators*, other than the principal investigator)

Dr Neil Davies
Dr Kyla Thomas
Dr Gemma Taylor
Dr Amy Taylor
Prof Richard Martin
Prof Frank Windmeijer
Prof Marcus Munafò.

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

6. Type of Institution (please tick one box below)

Academia ☒ Research Service Provider ☐ Pharmaceutical Industry ☐
NHS ☐ Government Departments ☐ Others ☐

7. Financial Sponsor of study

Pharmaceutical Industry *(please specify)* ☐ Academia*(please specify)* ☐
Government / NHS *(please specify)* ☒ NIHR None ☐
Other *(please specify)* ☐

8. Data source *(please tick one box below)*

Sponsor has on-line access ☐ Purchase of ad hoc dataset ☐
Commissioned study ☐
Other ☒ *(please specify)* Access through CPRD GOLD, currently being negotiated/arranged between the School of Social and Community Medicine and CPRD.

9. Has this protocol been peer reviewed by another Committee?

Yes* ☒ No ☐

This protocol has been peer reviewed as part of the NIHR HTA board's efficient study design call.

10. Type of Study *(please tick all the relevant boxes which apply)*

Adverse Drug Reaction/Drug Safety ☒ Drug Use ☐ Disease Epidemiology ☒
Drug Effectiveness ☒ Pharmacoeconomic ☐ Other ☐

11. This study is intended for:

Publication in peer reviewed journals ☒ Presentation at scientific conference ☒
Presentation at company/institutional meetings ☐ Other

12. Does this protocol also seek access to data held under the CPRD Data Linkage Scheme?

Yes ☒ No ☐

13. If you are seeking access to data held under the CPRD Data Linkage Scheme*, please select the source(s) of linked data being requested.

☒ Hospital Episode Statistics ☐ Cancer Registry Data**
☐ MINAP ☒ ONS Mortality Data
☒ Index of Multiple Deprivation/ Townsend Score
☐ Mother Baby Link ☐ Other: (please specify)

** As part of the ISAC review of linkages, the protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.*

***Please note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss this requirement further.*

14. If you are seeking access to data held under the CPRD Data Linkage Scheme, have you already discussed your request with a member of the Research team?

Yes ☒ No* ☐

**Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss your requirements before submitting your application.*

Please list below the name of the person/s at the CPRD with whom you have discussed your request.
James Ellis

15. If you are seeking access to data held under the CPRD Data Linkage Scheme, please provide the following information:

The number of linked datasets requested: 3

A synopsis of the purpose(s) for which the linkages are required:
To derive accurate outcome data -

Is linkage to a local dataset with <1 million patients being requested?

Yes* ☐ No ☒

** If yes, please provide further details:*

16. If you have requested linked data sets, please indicate whether the Principal Investigator or any of the collaborators listed in response to question 5 above, have access to any of the linked datasets in a patient identifiable form, or associated with a patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

17. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

** Please indicate what will be required:*
Completion of questionnaires by the GP Yes ☐ No ☐
Provision of anonymised records (e.g. hospital discharge summaries) Yes ☐ No ☐

Other (please describe)

ψ Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

18. Does this protocol describe a purely observational study using CPRD data (this may include the review of anonymised free text)?

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*
*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

19. Does this study involve linking to patient *identifiable* data from other sources?

Yes ☐ No ☒

20. Does this study require contact with patients in order for them to complete a questionnaire?

Yes ☐ No ☒

N.B. Any questionnaire for completion by patients must be approved by ISAC before circulation for completion.

21. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected*

22. Experience/expertise available

Please complete the following questions to indicate the experience/expertise available within the team of researchers actively involved in the proposed research, including analysis of data and interpretation of results

	Previous GPRD/CPRD Studies	Publications using GPRD/CPRD data
None	☐	☐
1-3	☐	☐
> 3	☒	☒

	Yes	No
Is statistical expertise available within the research team?	☒	☐

If yes, please outline level of experience

Three of the investigators have MScs in Epidemiology (KT, RM, AT), two have MScs in economics and econometrics (ND, FW) and two have MScs in psychology (MM, GT) and seven have epidemiology, econometrics, and psychology PhDs (ND, GT, KT, AT, FW, RM, MM).

Is experience of handling large data sets (>1 million records) available within the research team? ☒ ☐

If yes, please outline level of experience

Five previous published studies using CPRD data including validation studies and HES and ONS linkage data.

Is UK primary care experience available within the research team? ☒ ☐

If yes, please outline level of experience

RM has both worked as GPs and is a MRCGP.

23. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study.

1. K. H. Thomas *et al.*, Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. *BMJ*. **347**, f5704–f5704 (2013).
2. K. H. Thomas *et al.*, Validation of Suicide and Self-harm records in the Clinical Practice Research Datalink. *Br. J. Clin. Pharmacol.* (2012), doi:10.1111/bcp.12059.
3. N. M. Davies, G. Davey Smith, F. Windmeijer, R. M. Martin, COX-2 Selective Nonsteroidal Anti-inflammatory Drugs and Risk of Gastrointestinal Tract Complications and Myocardial Infarction: An Instrumental Variable Analysis. Epidemiology. 24, 352–362 (2013).

PROTOCOL CONTENT CHECKLIST

In order to help ensure that protocols submitted for review contain adequate information for protocol evaluation, ISAC have produced instructions on the content of protocols for research using CPRD data. These instructions are available on the CPRD website (www.cprd.com/ISAC). All protocols using CPRD data which are submitted for review by ISAC must contain information on the areas detailed in the instructions. IF you do not feel that a specific area required by ISAC is relevant for your protocol, you will need to justify this decision to ISAC.

Applicants must complete the checklist below to confirm that the protocol being submitted includes all the areas required by ISAC, or to provide justification where a required area is not considered to be relevant for a specific protocol. Protocols will not be circulated to ISAC for review until the checklist has been completed by the applicant.

Please note, your protocol will be returned to you if you do not complete this checklist, or if you answer 'no' and fail to include justification for the omission of any required area.

	Included in protocol?		
Required area	Yes	No	If no, reason for omission
Lay Summary (max.200 words)	☒	☐	
Background	☒	☐	
Objective, specific aims and rationale	☒	☐	
Study Type *Descriptive* *Hypothesis Generating* *Hypothesis Testing*	 ☒ ☐ ☒	 ☐ ☐ ☐	
Study Design	☒	☐	
Sample size/power calculation *(Please provide justification of sample size in the protocol)*	☒	☐	
Study population *(including estimate of expected number of relevant patients in the CPRD)*	☒	☐	
Selection of comparison group(s) or controls	☒	☐	
Exposures, outcomes and covariates *Exposures are clearly described* *Outcomes are clearly described*	☒ ☒ ☒	☐ ☐ ☐	
Use of linked data *(if applicable)*	☒	☐	
Data/ Statistical Analysis Plan *There is plan for addressing confounding* *There is a plan for addressing missing data*	☒ ☒ ☒	☐ ☐ ☐	
Patient/ user group involvement †	☒	☐	
Limitations of the study design, data sources and analytic methods	☒	☐	
Plans for disseminating and communicating study results	☒	☐	

† ***It is expected that many studies will benefit from the involvement of patient or user groups in their planning and refinement, and/or in the interpretation of the results and plans for further work. This is particularly, but not exclusively true of studies with interests in the impact on quality of life. Please indicate whether or not you intend to engage patients in any of the ways mentioned above.***

Voluntary registration of ISAC approved studies:

Epidemiological studies are increasingly being included in registries of research around the world, including those primarily set up for clinical trials. To increase awareness amongst researchers of ongoing research, ISAC encourages voluntary registration of epidemiological research conducted using MHRA databases. This will not replace information on ISAC approved protocols that may be published in its summary minutes or annual report. It is for the applicant to determine the most appropriate registry for their study. Please inform the ISAC secretariat that you have registered a protocol and provide the location.

What are the effects of varenicline compared with nicotine replacement therapy on long term smoking cessation and clinically important outcomes?

Investigators

Dr Neil Davies, Dr Kyla Thomas, Dr Gemma Taylor, Dr Amy Taylor, Prof Richard Martin, Prof Frank Windmeijer, and Prof Marcus Munafò.

Lay Summary

Smoking is a major avoidable cause of ill-health and premature death. Treatments which help patients successfully quit smoking could have an important effect on health and life expectancy. Varenicline is a medication that can help smokers successfully quit smoking. However, there are concerns that it may cause adverse effects, such as increase in depression, self harm and suicide, and in cardiovascular disease events. In this project we will investigate the effects of varenicline compared to nicotine replacement therapies on: i) long-term smoking cessation and whether the effects differ by area level deprivation; and ii) the following clinically-important outcomes: rate of GP and hospital attendance; all-cause mortality and death due to diseases of the respiratory system and cardiovascular disease; and a primary care diagnosis of respiratory illness, myocardial infarction or depression and anxiety. The study is based on a cohort of patients prescribed these smoking cessation medications from the Clinical Practice Research Datalink (CPRD).

Aims and Objectives

1. To investigate the long-term smoking abstinence of patients prescribed either varenicline or nicotine replacement products in the CPRD and whether the effects differ by:
    a. area level deprivation;
    b. multiple nicotine replacement products compared to monotherapy;
    c. the duration of smoking cessation therapy treatment; and
    d. whether patients have already had one unsuccessful quit attempt during their first round of therapy.
2. To investigate the causal effects of prescribing smoking cessation therapies on:
    a. frequency of GP and hospital attendance,
    b. frequency of all-cause and cause-specific hospitalisation (specifically diseases of the respiratory system, cardiovascular disease and mental disorders),
    c. all-cause mortality and death due to diseases of respiratory system, cardiovascular disease and mental disorders,
    d. incident diagnosis of respiratory illness,
    e. incident diagnosis of myocardial infarction, and
    f. incident diagnosis of depression or anxiety.

Background and rationale

Smoking is the major avoidable cause of preventable morbidity and mortality in the UK and internationally (*1*, *2*). Smoking is also the principal cause of health inequalities and is responsible for most of the difference in healthy life-expectancy between the richest and poorest in our society (*3*) and those with and without mental health problems (*4*). It has been estimated that smoking-related illnesses cost the NHS approximately £5bn per year (*5*). Varenicline has been shown to be the most clinically effective smoking cessation medicine for short-term abstinence in randomized controlled trials (RCTs) (*6*). However, there is

relatively little evidence for its long-term effectiveness and impact on clinical outcomes which are relevant to the NHS.

Concerns have been raised that varenicline is associated with a higher risk of adverse events, including suicide and self-harm and cardiovascular events, than other smoking cessation interventions (*7*). This has led the Food and Drug Administration (FDA) to issue black box warnings about the possible adverse effects of varenicline (*8*). However, much of the evidence about the potential adverse effects of varenicline comes from observational studies which are prone to confounding. This project will add to the evidence base about the possible adverse and beneficial effects of prescribing different smoking cessation medications using three statistical approaches to overcome confounding: multivariable adjusted regression, propensity score regression and instrumental variable analysis.

We will investigate the effects of varenicline on smoking abstinence because existing evidence from randomised controlled trials typically only followed participants for a year, and are not informative about longer term outcomes. We will investigate the effects of varenicline prescriptions on all-cause primary and secondary care utilization because smoking increases morbidity and imposes major costs on the health care services (*9*). We will examine differences in smoking cessation medication effectiveness by socio-economic position because a recent systematic review reported that NHS stop-smoking services may be helping to reduce inequalities in smoking prevalence by preferentially targeting smokers of lower socio-economic position (SEP) and data from primary care records (THIN) show that between 2008 and 2010, smokers in more deprived groups were more likely to receive smoking cessation interventions (*10*).

We will not investigate bupropion because it is rarely prescribed and systematic reviews have found that it is less effective than varenicline for smoking cessation (*6*).

We will investigate the effects of varenicline on cardiovascular outcomes because previous research has suggested that patients prescribed varenicline may have higher rates of cardiovascular disease (*11*, *12*). We will investigate the effects of varenicline on respiratory illnesses because smokers are at higher risks of these outcomes. We will investigate the effects of varenicline on depression and anxiety because there has been some reports that varenicline may reduce the risk of depression and anxiety (*7*).

We will investigate the incidence of each of these illnesses using primary care diagnoses based on Read codes; admission to secondary care using ICD-10 codes; and ONS mortality records. This will maximise the number of events we detect. We will use validated code lists for each outcomes, as listed in the outcomes section of this protocol for further details.

Plan of Investigation

We will use the CPRD to conduct a cohort study of all patients prescribed varenicline or nicotine replacement products. Exposure will be defined as the first prescription of either varenicline or nicotine replacement therapy. We will investigate differences in the outcomes described above.

For the statistical analysis we will use Cox-regression models adjusted for a range of baseline confounders, propensity score matched Cox-regression, and instrumental variable analyses using physicians' prescribing preferences as instruments for the prescriptions issued.(*13*, *14*)

Study design and type

Hypothesis testing observational cohort study employing causal analysis methods.

Setting/Context
Prescriptions of varenicline and nicotine replacement products issued in primary care.

Target population
All smokers aged over 18 prescribed smoking cessation treatment in eligible primary care centres contributing to the CPRD after the 1st of September 2006, when varenicline was introduced.

Sampling
We will sample all individuals prescribed smoking cessation medication at any point after 1st of September 2006 to the most recent release of the CPRD data.

Study population
We will use patients prescribed other smoking cessation products (nicotine patches and gum) as controls for patients prescribed varenicline.

Inclusion Criteria
Patients who were older than 18, who were prescribed medicines in BNF category 4.10.2 from 1st September 2006, when varenicline was introduced to the UK, to the present**.**

Records from patients classified as 'acceptable' by the CPRD from **all** up to standard practices at least 18 months prior to date of entry of each cohort (1st January 2005). Patient data are defined as "acceptable" by the CPRD if they meet minimum quality control standards, for example their registration period with their GP is valid.

Exclusion Criteria
Patients who registered at a practice less than 365 days before the first recorded prescription, to allow for high quality assessment of baseline data and possible confounders. Patients prescribed bupropion in the year before their index prescription of varenicline or NRT will be excluded from the analysis. In the primary analysis we will exclude patients initially prescribed both nicotine replacement therapies and varenicline together, although in our previous analysis this only occurred for 0.25% of all prescriptions.

Follow-up
Follow-up will end with the earliest of either a pre-specified outcome event or censoring due to the end of registration.

Power calculations
The following power calculations are based on effect sizes and confidence intervals observed in our previous analyses, which had data on 110,000 individuals prescribed either varenicline or nicotine replacement therapy (*7*). Based on the rate of 18,000 new prescriptions per year observed in the CPRD from 2006 to 2011 (*7*), we estimate that with a further 4 years of follow-up the number of patients prescribed either varenicline or nicotine replacement therapy will have increased by 72,000. Therefore the total expected sample size for analysis will be around 180,000.

In our previous analysis using CPRD data the age- and sex-adjusted hazard ratio for self-harm/suicide for varenicline vs. nicotine replacement therapy at nine months was 0.73 (95% CI: 0.54 to 0.99); after adjusting for possible confounders this became: 0.90 (95% CI: 0.66 to 1.22) (*7*). A 70% increase in sample size would lead to a reduction of the standard error by a factor of 1.3, reducing the breadth of the above-adjusted confidence interval from 0.56 to 0.43.

Rare outcomes, self-harm and suicide, were used in previous analyses; we will have greater power to explore more common outcome measures within this project. For example, in the previous analysis the nine month age- and sex-adjusted hazard ratio for all-cause mortality nine months after first prescription for varenicline vs. nicotine replacement therapy was 0.43 (95% CI: 0.35 to 0.53); after controlling for possible confounders this became: 0.49 (95% CI: 0.40 to 0.61). A 70% increase in sample size would lead to a reduction of the standard error by a factor of 1.3, reducing the breadth of the above-adjusted confidence interval from 0.21 to 0.16.

For the effects of varenicline versus nicotine replacement therapy on all-cause mortality, instrumental variable analysis found a risk difference of 0.7 (95% CI: -3.3 to 4.7) per 1,000 patients treated after nine months. We estimate that a 70% increase in sample size would narrow the confidence intervals from 8.0 to 6.2.

Using data from our previous project, within two years of first prescription, we found 2,517 admissions for respiratory disease amongst 1374 patients; 3,144 admissions for cardiovascular disease amongst 1022 patients; and 3,277 admissions for depression or anxiety amongst 213 patients. This is more events than we found for suicide and self-harm in our previous study; therefore we believe there will be enough events for this analysis.

This work builds upon the work conducted previously in CPRD (protocol number: 10_165) and will be conducted in parallel with a related proposal (funded by GRAND, PI Dr. Amy Taylor) investigating the impact of smoking cessation medication on specific mental health outcomes.

To investigate differences in health care seeking behaviour of smokers by socioeconomic position we will combine the sample used for Aims 1 & 2 above with a sample of all other patients indicated as a current smoker after the 1st of September 2006. We will define smoking status using the additional data table. These will be patients who have a smoking record (enttype=4) which indicates current smoker (data1 field=1 “Yes”) after the 1st of September 2006.

Data collection and analysis
We will use the latest available release of the CPRD. This is because General Practices enrolled with the CPRD send regular tranches of data which are released to researchers throughout the year. This will guarantee that we have the largest possible sample of patients for our analysis.

Data linkage
We will use linked HES and ONS mortality data to define the outcomes for aims 2.a, 2.b, and 2.c (frequency of GP and hospital attendance, frequency of all-cause and cause-specific hospitalization and all-cause and cause-specific mortality). We will test these hypotheses using data from linked practices only.

These are important hard outcomes for our study. We have already established that for certain outcomes, such as cause specific mortality the linked ONS data is more accurate (*15*).Whilst it is possible to investigate these outcomes using CPRD data from general practices, the data are less precise and consistently recorded. Thus analyses using linked data are likely to be more precise. Furthermore, the linked data provide direct evidence about secondary care attendance of patients via the HES data. Again, whilst there is some data about referrals to secondary care in the main tables of the CPRD, the data are not as comprehensive as HES data. Our outcomes of interest occur after September 2006; therefore we believe that both the linked HES and ONS data will provide sufficient coverage for these outcomes.

Exposures, outcomes and covariates definitions

Exposures

First time users of the smoking cessation therapies (varenicline or nicotine replacement therapy) will be defined as people who received at least one prescription of the product after the 1st of September 2006 but with no use of a related product during the 12 months before the index date (the first date on which a prescription was issued). Langley et al. (2010) found the smoking cessation prescription data in the THIN database, which is closely related to the CPRD, to be highly comparable to national dispensing data (*16*). The analysis will be limited to the first treatment episode. This will mimic an intention to treat analysis in a RCT (*17*). This ensures that the target parameter estimated in the observational study will be comparable to the parameter estimated by a RCT. The prescriptions will be defined by the therapy file in the CPRD, which contains a list of all prescriptions issued to patients at the practices. Each therapy record records the date a prescription was issued, the quantity of drug prescribed and the dosage.

To mimic an intention-to-treat analysis in an RCT in our primary analysis patients who are initially prescribed nicotine replacement therapy, but later switch to varenicline, will be allocated to nicotine replacement therapy and vice-versa. We will use an intention to treat design for two reasons. First, whilst there are theoretical statistical models for estimating the effects of treatment switching such as marginal structural models, these methods require the strong assumption that there is no unmeasured confounders and typically require detailed data on time-varying confounders which are unlikely to be available in the CPRD. Second, to our knowledge there are no instrumental variable methods for estimate the effects of switching treatment. Appendix 1 provides code lists defining varenicline and nicotine replacement therapy prescriptions.

Outcomes

Outcome 1: Smoking abstinence

In the CPRD smoking status is indicated in the additional data tables as whether the patient is a current, former or never smoker. As GPs are paid to record smoking status smoking behaviour is robustly recorded in the CPRD (*18*). Marston et al. (2014) found that 84% of patients had smoking status recorded within a year of registering at a practice, and that smoking prevalence rates by age were similar in CPRD and the Health Survey of England (*18*). Booth et al. (2013) found that the difference in prevalence of smoking estimate between the CPRD and the Health Survey for England was less than 1%, and the mean difference was

0.1% (95% CI: -1.5% to 1.7%) (*19*). Using unpublished data from CPRD sampled as part of the research reported in Thomas et al. (2013) we found that 74% of patients prescribed smoking cessation medication had a subsequent record indicating smoking status. Of these 66% were indicated as current smokers and 33% as ex-smokers. We will initially define a patient as relapsed if they have any record indicating that the patient is a current smoker after their first prescription of a smoking cessation therapy. We will not be able to determine the smoking status of patients who do not return to the GP. Therefore, we will perform sensitivity analyses to examine whether the assumptions made about the smoking status of individuals who are not observed affect the results. For example, we will conduct a sensitivity analysis to see if the results are altered by assuming that patients with missing data have relapsed, or by assuming that patients with missing outcomes have achieved abstinence.

Outcome 2: GP and hospital attendance

We will define service use as any attendance to hospitals and more than the median number of attendances to the GP in the 3, 6, 9, 12, 24 and 48 months after first prescription. We will define GP appointments using the clinical data file of the CPRD. This includes all the diagnoses and symptoms that GPs record about all of their patients. As with the other outcomes, the vast majority of diagnoses and symptoms include the date on which the data were added to the database. We will use these dates to calculate the time to event. We will define the hospital visits outcome using the linked Hospital Episodes Statistics data. We will investigate all-cause hospitalisation and three specific causes of hospitalisation: 1) diseases of respiratory system (ICD-10=J00-J99), 2) cardiovascular disease (ICD-10=I00-I52) and 3) anxiety and depression (ICD-10=F31.3, F31.4, F31.5, F32, F40-F48).This is available for approximately half of the sample. Again these data contain the date on which the event occurred, which we will use to define attendance to secondary care within 3, 6, 9, 12, 24 and 48 months after first prescription.

Outcome 3: All-cause and cause-specific mortality

We will define all-cause and cause-specific mortality using the linked Office of National Statistics mortality dataset. These include the date of death and cause of death using ICD-9 codes. We will investigate three specific causes of mortality, 1) diseases of respiratory system (ICD-10=J00-J99), 2) cardiovascular disease (ICD-10=I00-I52) and 3) anxiety and depression (ICD-10=F31.3, F31.4, F31.5, F32, F40-F48). Our primary outcome for the entire study is all-cause mortality.

Outcome 4: Incident respiratory illness, myocardial infarction, depression or anxiety

We will define the adverse event outcomes using the diagnosis records from the Clinical and Referral files in the CPRD. These files record all the diagnoses that the GPs input into their computer system. Each record in the table is given a diagnosis code based on the Read code categorisation. We will use validated Read code lists, for the three adverse event outcomes, respiratory illnesses, myocardial infarction or depression and anxiety, please see the cited papers and appendix 2 for Read code lists (*20–22*). For eligible patients we will extract all records from the Clinical and Referral Tables that indicate the patient either received a specific diagnosis or were referred for a specific diagnosis. As with the therapy records for prescriptions described above, each Clinical and Referral Record indicates the date the information was inputted into the system. We will use this date to define the date that the diagnosis was made. We will define a set of outcomes within 3, 6, 9, 12, 24 and 48 months after first prescription.

Covariates

We will include gender, age in years at time of first prescription, previous psychiatric illness/consultation, previous use of psychotropic medications such as hypnotics, antipsychotics and antidepressants (defined by BNF 4.1, 4.2, and 4.3), previous self-harm (see appendix 3), measures of alcohol consumption where appropriate mean/median number of GP visits per year, body mass index, socioeconomic position (deprivation score for area or residence) and major chronic illness (including diabetes, cancer, arthritis) using the Charlson index (for code lists see *25, 26*). Collider bias could occur if we conditioned on events which happened as a result of the prescription the patient was issued. To prevent this bias from affecting our results, we will define each covariate using data inputted prior to the first prescription (*25*). If there are missing data in the covariates we will consider using multiple imputation.

Statistical Analysis

For investigating the effects of varenicline use on each outcome (long-term smoking cessation, frequency of GP and hospital attendance, all-cause and cause-specific mortality, primary care diagnosis of respiratory illness, myocardial infarction, depression or anxiety), we will report a conventional multivariable-adjusted Cox regression, propensity score regression and instrumental variable analysis.

A. Conventional Cox-regression

In our first analysis, a conventional observational analysis, we will estimate hazard ratios of the outcomes using Cox-proportional hazards models and the actual prescriptions issued to the patients (*26*). Each patient's date of entry into the cohort will be the date they were first prescribed a smoking cessation therapy. The date of exit for each outcome will be the date on which they first have an event, or are censored due to end of follow-up or death or leaving the practice. We will report these associations adjusted for basic confounders (age and gender), and results adjusted for all measured covariates described above.

B. Propensity score regression

In our second analysis we will construct a sample of patients balanced on covariates and risk factors using a propensity score (*27–30*). We will construct propensity scores using a logistic regression of the actual treatment received on the covariates described above. Therefore, each participant's propensity score will be their conditional probability (odds) of receiving varenicline versus nicotine replacement therapy. We will match each patient receiving varenicline to another patient receiving nicotine replacement therapy with the closest propensity score on a ratio of 1:1 using a nearest neighbour algorithm with no replacement, and matching will be restricted to the common support region. Patients outside the common support region are those prescribed varenicline with propensity scores higher than any patient prescribed nicotine replacement therapy and vice versa. We will estimate hazard ratios of the outcomes using the propensity score matched sample using Cox-regressions using the same entry and exit information as the conventional Cox-regression analysis described above.

C. Instrumental variable analysis

In our third analysis, we will estimate the effects of smoking cessation therapies on the outcomes using physicians' prescribing preferences as instruments for the prescriptions the GPs issue to their patients. We cannot directly measure the physicians' preferences; therefore we will use the prescriptions they issued to their previous patients as a proxy for their preferences. For example, if the instrument was based on just one previous prescription,

physicians who previously prescribed varenicline would categorised as a varenicline prescriber. See **Section 2** for further details. As with our previous studies we will use seven prior prescriptions to improve the strength of the instruments (*7*, *14*, *31*). Using multiple prior prescriptions will maximise power. We will report risk differences in the outcomes using additive structural mean models estimated via the generalised method of moments (*32–34*).

We will categorise each of the adverse event outcomes as occurring within 3, 6, 9, 12, 24 and 48 months of first prescription. We will do this because methods for conducting survival analysis using instrumental variables are not well developed. We will use Stata 13.1 SE to generate all results. The instrumental variable analysis will be conducted using the ivreg2 command and psmatch2 will be used to construct the propensity score (*28*, *35*, *36*). All standard errors will be estimated using cluster robust standard errors which accounts for clustering of patients within practices.

D. Socio-economic variation in effectiveness of smoking cessation treatments

This project will use the entire sample of patients indicated as a smoker at any point after 1st September 2006. We will assign a measure of area level deprivation to each patient using their home address postcode and to each GP practice using the practice postcode. Deprivation levels will be based on the Indices of Multiple Deprivation (IMD) which are available from the Office of National Statistics. IMD statistics are updated every two years. We will use the most recent IMD statistics preceding the date of entry into the study for each patient. Although area level deprivation statistics will only be a proxy for individual level deprivation, these demonstrate the expected associations with smoking prevalence (*37*).

We will investigate whether the proportion of smokers who attend their GP for smoking cessation treatment differs by IMD, and whether there are any differences in prescribing of varenicline versus nicotine replacement products between areas of high and low deprivation.

By using both individual and GP level IMD codes, we will investigate whether the effects of smoking cessation therapies differ by IMD at both the level of GP practice and at the individual level. We will investigate treatment compliance by reporting the total number of prescriptions issued after the initial prescription.

We will estimate the effects of smoking cessation therapies within sub-groups defined by IMD level both at the individual and practice level using the three methods described above, multivariable-adjusted Cox regression, propensity score regression and instrumental variable analysis (*26*, *29*, *38*). The cohort of patients will be defined as described above. We will report these associations adjusted for basic confounders (age and gender), and results adjusted for all measured covariates described above. Analyses will account for clustering of patients by GP practice.

Patient or user group involvement

Participants of the UK Centre for Tobacco and Alcohol Studies Smokers' Panel reviewed our research proposal. The Smokers' Panel consists of 25 current smokers and recent quitters, based in Bath. This panel meets twice a year, each time focussing on a theme with presentations from Centre members, students and external colleagues. Proceedings are taped and transcribed, and ideas and feedback used to identify new research questions, write new grant proposals, and ensure accessible language use in publications and study materials. Panel members also contribute to the design and provision of a service user perspective in teaching,

have attended and spoken at events and conferences, and one serves on a NICE Programme Development Group. The smokers' panel meet twice a year and in between meetings, panel members are involved with UKCTAS researchers in developing ideas for research, commenting on proposals and participating in studies.

Dr. Thomas presented an outline of our proposal to the Elizabeth Blackwell Institute's (EBI) Public Advisory Group (http://www.bristol.ac.uk/blackwell/about/organisation/public-advisory/). This is a panel of lay members of the public who advise researchers at the EBI. The panel provided comments on the proposal. They suggested potential novel avenues for dissemination via local organisations such as Bristol City Council, including: smoking cessation groups; initiatives such as the Wellbeing Charter (http://www.wellbeingcharter.org.uk/); local media, such as Dr. Philip Hammond on BBC radio; and disseminating information directly to smoking advisors associated with pharmacies and GP practices.

Involvement during the project

During the course of the project the PI and RA will meet with the UKCTAS smokers' panel three times. In the first month we will meet to describe our plans for the research and allow the panel to provide feedback about our research protocol. The PI and RA will meet with the smokers' panel again after nine months, when we will discuss the preliminary results and respond to comments and suggestions. We will meet a final time towards the end of the project to discuss the plans for dissemination and future work.

As part of our proposal we requested resources to pay for lay members of the public to review and provide feedback on our conferences presentations and manuscripts.

We will also obtain feedback on our plans from the Elizabeth Blackwell Institute's (EBI) Public Advisory Group. As with the UKCTAS panel, we will consult with EBI panel three times over the course of the project, getting feedback on our objectives, our results, and our plans for dissemination and future research.

Limitations of the study design, data sources and analytic methods

This analysis has the following limitations:

1. This is an observational study – any difference between products could arise because of uncontrolled confounding. We will investigate such effects by comparing the characteristics of those prescribed different products and adjusting for any differences in multivariable models and exploring different approaches for modeling confounding by indication.

2. It is restricted to products prescribed in primary care, so for example patients receiving smoking cessation products in NHS smoking cessation clinics or buying over-the-counter nicotine replacement products from pharmacies will be excluded. Patients receiving prescriptions for nicotine replacement products are likely to be poorer than those who chose to buy these products over the counter. Furthermore those visiting their GP for prescriptions of smoking cessation products may differ from those attending specific smoking cessation clinics, meaning findings may not be generalisable to the wider population of people taking smoking cessation aids. We will compare the characteristics of patients prescribed the various study drugs to assess differences and control for differences in the analysis.

3.People taking varenicline may be more likely to have already tried (and failed) to stop smoking with nicotine replacement therapy and so differ in underlying characteristics / level of addiction compared to those prescribed nicotine replacement products. This may

exaggerate any difference between risks associated with nicotine replacement products and bupropion / varenicline.

5. It is possible that some patients are prescribed different smoking cessation within the study period. Furthermore there may be a hierarchy of treatment i.e patients being prescribed nicotine replacement therapies first and only if this fails being moved onto varenicline. Thus patients prescribed varenicline may represent more addicted smokers and this in turn may be at greater risk of adverse outcomes. We will explore methods to model the effects of time dependent switching between products.

6. Prescribing patterns may have changed following specific drug scares. For example a varenicline scare may push GPs towards prescribing nicotine replacement therapies for high risk patients, introducing selection bias.

Peer Review

This protocol has been peer reviewed separately as part of the NIHR Health Technology Assessment board's efficient study designs call (proposal ID 14/49/94).

Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication.

Key findings will be collated to form evidence based recommendations which will be communicated to relevant groups, with the aim of improving the evidence base to inform advice to prescribers and patients. We will also aim to publish findings in peer reviewed journals and present our work at national and international conferences.

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Appendix 1: Varenicline and nicotine replacement therapy code list

prodcode	multilexcode	productname	drugsubstancename
10527	2259002	NICABATE patch 14mg [MERRELL]	nicotine
7644	2259003	NICABATE patch 21mg [MERRELL]	nicotine
10623	2259001	NICABATE patch 7mg [MERRELL]	nicotine
29680	1418002	NICONIL patch 11mg/24 hr [ELANPHARMA]	nicotine
27311	1418001	NICONIL patch 22mg/24 hr [ELANPHARMA]	nicotine
37716	15557001	NICOPASS lozenge 1.5mg [WOCKHARDT]	nicotine
36635	15531001	NICOPATCH patch 14mg/24 hours [WOCKHARDT]	nicotine
36457	15533001	NICOPATCH patch 21mg/24 hours [WOCKHARDT]	nicotine
36618	15530001	NICOPATCH patch 7mg/24 hours [WOCKHARDT]	nicotine
2876	1095001	NICORETTE chewing gum 2mg [PHARMACIA]	nicotine
4166	1095002	NICORETTE chewing gum 4mg [PHARMACIA]	nicotine
5320	11711001	NICORETTE inhalator cartridge 10mg [MCNEIL]	nicotine
39046	16729001	NICORETTE INVISI patch 25mg [MCNEIL]	nicotine
5877	7158002	NICORETTE microtab 2mg [PHARMACIA]	nicotine
25523	7158001	NICORETTE mint flavour chewing gum 2mg [PHARMACIA]	nicotine
31939	1095003	NICORETTE mint plus chewing gum 4mg [PHARMACIA]	nicotine
1248	7342001	NICORETTE nasal spray 10mg/ml [PHARMACIA]	nicotine
5440	2236002	NICORETTE patch 10mg [PHARMACIA]	nicotine
1703	2236003	NICORETTE patch 15mg [PHARMACIA]	nicotine
6018	2236001	NICORETTE patch 5mg [PHARMACIA]	nicotine
5944	11708001	nicotine cartridge - (for inhalation) 10mg	nicotine
6323	4272001	nicotine chewing gum 2mg	nicotine
5758	4272002	nicotine chewing gum 4mg	nicotine
25510	7159001	nicotine mint flavour chewing gum 2mg	nicotine
25516	4272003	nicotine mint flavour chewing gum 4mg	nicotine
8571	7163001	nicotine nasal spray 10mg/ml	nicotine
5479	2260002	nicotine patch 10mg	nicotine
9591	2326002	nicotine patch 14mg	nicotine
5502	2260003	nicotine patch 15mg	nicotine
6448	2326003	nicotine patch 21mg	nicotine
33392	7107001	nicotine patch 22mg/24 hr	nicotine
5457	2260001	nicotine patch 5mg	nicotine
9804	2326001	nicotine patch 7mg	nicotine
11718	7159003	nicotine sublingual tablets 2mg	nicotine
37646	15556001	nicotine sugar free lozenge 1.5mg	nicotine
5515	1569001	nicotine sugar free lozenge 1mg	nicotine
9806	8837001	nicotine sugar free lozenge 2mg	nicotine
5784	1917001	nicotine sugar free lozenge 4mg	nicotine
5946	8751001	NICOTINELL chewing gum 2mg [NOVARTIS]	nicotine
13048	8751002	NICOTINELL chewing gum 4mg [NOVARTIS]	nicotine
5531	8751003	NICOTINELL lozenge 1mg [NOVARTIS]	nicotine
38958	16673001	NICOTINELL MINT lozenge 1mg [NOVARTIS]	nicotine

6698	12077001	NICOTINELL MINT lozenge 2mg [NOVARTIS]	nicotine
7303	2262001	NICOTINELL TTS patch 10 square cm [NOVARTIS]	nicotine
5606	2262002	NICOTINELL TTS patch 20 square cm [NOVARTIS]	nicotine
3818	2262003	NICOTINELL TTS patch 30 square cm [NOVARTIS]	nicotine
6565	10887001	NIQUITIN chewing gum 2mg [GLAXSK CON]	nicotine
6642	10889001	NIQUITIN chewing gum 4mg [GLAXSK CON]	nicotine
5700	8615001	NIQUITIN lozenge 2mg [GLAXSK CON]	nicotine
5659	8151001	NIQUITIN lozenge 4mg [GLAXSK CON]	nicotine
6630	12079001	NIQUITIN MINT lozenge 2mg [GLAXSK CON]	nicotine
6593	12080001	NIQUITIN MINT lozenge 4mg [GLAXSK CON]	nicotine
4717	11994002	NIQUITIN patch 14mg [GLAXSK CON]	nicotine
3404	11994003	NIQUITIN patch 21mg [GLAXSK CON]	nicotine
4704	11994001	NIQUITIN patch 7mg [GLAXSK CON]	nicotine
39166	16728001	NICORETTE INVISI patch 15mg [MCNEIL]	nicotine
39123	16726001	nicotine patch 25mg	nicotine
39521	16698001	NIQUITIN PRE-QUIT MINT lozenge 4mg [GLAXSK CON]	nicotine
39572	16727001	NICORETTE INVISI patch 10mg [MCNEIL]	nicotine
40617	17228001	NICOTINELL 20 TTS patch 14mg/24 hours [NOVARTIS]	nicotine
40620	17229001	NICOTINELL 30 TTS patch 21mg/24 hours [NOVARTIS]	nicotine
40683	17276001	NICOTINELL 10 TTS patch 7mg/24 hours [NOVARTIS]	nicotine
40730	17292001	NIQUITIN MINIS MINT lozenge 1.5mg [GLAXSK CON]	nicotine
40865	17293001	NIQUITIN MINIS MINT lozenge 4mg [GLAXSK CON]	nicotine
41040	17396001	NICORETTE LEMON microtab 2mg [MCNEIL]	nicotine
41377	17493001	NICORETTE chewing gum 2mg [MCNEIL]	nicotine
41753	17498001	NICORETTE chewing gum 4mg [MCNEIL]	nicotine
41778	17500001	NICORETTE FRESHFRUIT chewing gum 4mg [MCNEIL]	nicotine
41801	17495001	NICORETTE FRESHMINT chewing gum 2mg [MCNEIL]	nicotine
41425	17501001	NICORETTE FRESHMINT chewing gum 4mg [MCNEIL]	nicotine
41779	17496001	NICORETTE ICY WHITE chewing gum 2mg [MCNEIL]	nicotine
41493	17502001	NICORETTE ICY WHITE chewing gum 4mg [MCNEIL]	nicotine
41356	17499001	NICORETTE microtab 2mg [MCNEIL]	nicotine
41809	17503001	NICORETTE MINT chewing gum 4mg [MCNEIL]	nicotine
41496	17509001	NICORETTE nasal spray 10mg/ml [MCNEIL]	nicotine
41474	17505001	NICORETTE patch 10mg [MCNEIL]	nicotine
41376	17507001	NICORETTE patch 15mg [MCNEIL]	nicotine
41802	17504001	NICORETTE patch 5mg [MCNEIL]	nicotine
41808	17528001	NICOTINELL FRUIT chewing gum 4mg [NOVARTIS]	nicotine
41765	17526001	NICOTINELL MINT chewing gum 2mg [NOVARTIS]	nicotine
41505	17490001	NIQUITIN CLEAR patch 14mg [GLAXSK CON]	nicotine
41372	17492001	NIQUITIN CLEAR patch 21mg [GLAXSK CON]	nicotine
41507	17487001	NIQUITIN CLEAR patch 7mg [GLAXSK CON]	nicotine
41485	17489001	NIQUITIN patch 14mg [GLAXSK CON]	nicotine
41368	17491001	NIQUITIN patch 21mg [GLAXSK CON]	nicotine
41426	17488001	NIQUITIN patch 7mg [GLAXSK CON]	nicotine
41864	17494001	NICORETTE FRESHFRUIT chewing gum 2mg [MCNEIL]	nicotine
42016	17497001	NICORETTE MINT chewing gum 2mg [MCNEIL]	nicotine

41860	17395001	nicotine bitartrate sublingual tablets 2mg	nicotine
42048	17472001	nicotine bitartrate sugar free lozenge 1mg	nicotine
41923	17570001	nicotine patch and gum 15mg + 2mg	nicotine
41881	17523001	NICOTINELL CLASSIC chewing gum 2mg [NOVARTIS]	nicotine
42011	17527001	NICOTINELL CLASSIC chewing gum 4mg [NOVARTIS]	nicotine
41931	17524001	NICOTINELL FRUIT chewing gum 2mg [NOVARTIS]	nicotine
41879	17525001	NICOTINELL LIQUORICE chewing gum 2mg [NOVARTIS]	nicotine
42047	17529001	NICOTINELL LIQUORICE chewing gum 4mg [NOVARTIS]	nicotine
41909	17530001	NICOTINELL MINT chewing gum 4mg [NOVARTIS]	nicotine
42400	17571001	NICORETTE COMBI patch and gum [MCNEIL]	nicotine
42286	17473001	nicotine bitartrate sugar free lozenge 2mg	nicotine
42221	7111009	NICOTINE lozenge 4mg [TEVA]	nicotine
44106	18071001	NIQUITIN MINIS CHERRY lozenge 1.5mg [GLAXSK CON]	nicotine
45603	18423001	NICORETTE FRESHMINT lozenge sugar-free 2mg [MCNEIL]	nicotine
45504	18428001	nicotine mouth spray 1mg/dose	nicotine
45429	18429001	NICORETTE QUICKMIST mouth spray 1mg/dose [MCNEIL]	nicotine
46588	18778001	NICOTINELL ICEMINT chewing gum 2mg [NOVARTIS]	nicotine
46592	18826001	NICORETTE inhalator cartridge 15mg [MCNEIL]	nicotine
46701	18779001	NICOTINELL ICEMINT chewing gum 4mg [NOVARTIS]	nicotine
46717	18825001	nicotine cartridge - (for inhalation) 15mg	nicotine
27414	14599001	varenicline tablets 1mg	varenicline tartrate
27411	14602001	CHAMPIX film coated tablets 1mg [PFIZER]	varenicline tartrate
27412	14596001	varenicline tablets 500micrograms + 1mg	varenicline tartrate
27410	14600001	CHAMPIX film coated tablets 500micrograms + 1mg [PFIZER]	varenicline tartrate
35089	14598001	varenicline tablets 500 micrograms	varenicline tartrate
35035	14601001	CHAMPIX film coated tablets 500 micrograms [PFIZER]	varenicline tartrate

Appendix 2: Read code list to identify depression

medcode	readcode	readterm
324	E2B..00	Depressive disorder NEC
12450	6896	Depression screening using questions
543	Eu32z11	[X]Depression NOS
655	E200300	Anxiety with depression
1996	1B17.00	Depressed
4824	1B17.11	C/O - feeling depressed
1131	E204.00	Neurotic depression reactive type
4639	Eu32.00	[X]Depressive episode
10015	1BT..00	Depressed mood
30405	9H92.00	Depression interim review
1908	2257	O/E - depressed
9796	1B1U.00	Symptoms of depression
2639	E204.11	Postnatal depression
6932	E113.11	Endogenous depression - recurrent
2970	Eu32z00	[X]Depressive episode, unspecified
5987	Eu32z14	[X] Reactive depression NOS
6950	E112.13	Endogenous depression first episode
9211	Eu32100	[X]Moderate depressive episode
595	E112.14	Endogenous depression
5879	E112.11	Agitated depression
1055	E135.00	Agitated depression
4323	E2B1.00	Chronic depression
10610	E112.00	Single major depressive episode
11717	Eu32000	[X]Mild depressive episode
6482	E113700	Recurrent depression
19439	212S.00	Depression resolved
3292	Eu33.00	[X]Recurrent depressive disorder
11913	Eu41200	[X]Mixed anxiety and depressive disorder
10438	1B1U.11	Depressive symptoms
15099	E113.00	Recurrent major depressive episode
3291	Eu32z12	[X]Depressive disorder NOS
9667	Eu32200	[X]Severe depressive episode without psychotic symptoms
6546	E112.12	Endogenous depression first episode
9055	Eu32.11	[X]Single episode of depressive reaction
10667	Eu32400	[X]Mild depression
14709	E113200	Recurrent major depressive episodes, moderate
2560	E11..12	Depressive psychoses
16506	E112100	Single major depressive episode, mild
7604	Eu32.13	[X]Single episode of reactive depression
15220	Eu34114	[X]Persistant anxiety depression
15155	E112200	Single major depressive episode, moderate
1533	E290.00	Brief depressive reaction
29520	Eu33100	[X]Recurrent depressive disorder, current episode moderate
9183	E11z200	Masked depression

7749	Eu41211	[X]Mild anxiety depression
12099	Eu32300	[X]Severe depressive episode with psychotic symptoms
8902	Eu33.13	[X]Recurrent episodes of reactive depression
13307	Eu53011	[X]Postnatal depression NOS
8851	Eu33.11	[X]Recurrent episodes of depressive reaction
10455	E211200	Depressive personality disorder
7011	E112z00	Single major depressive episode NOS
16632	E291.00	Prolonged depressive reaction
7737	Eu34113	[X]Neurotic depression
25563	E113z00	Recurrent major depressive episode NOS
17770	E130.11	Psychotic reactive depression
6854	Eu32y00	[X]Other depressive episodes
44300	Eu33z00	[X]Recurrent depressive disorder, unspecified
29342	E113100	Recurrent major depressive episodes, mild
29784	Eu33000	[X]Recurrent depressive disorder, current episode mild
8584	Eu34111	[X]Depressive neurosis
15219	E112300	Single major depressive episode, severe, without psychosis
33469	Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt
8478	E130.00	Reactive depressive psychosis
22806	Eu32212	[X]Single episode major depression w'out psychotic symptoms
25697	E113300	Recurrent major depressive episodes, severe, no psychosis
11329	Eu33211	[X]Endogenous depression without psychotic symptoms
34390	E112000	Single major depressive episode, unspecified
47009	Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp
55384	E113600	Recurrent major depressive episodes, in full remission
19696	Eu33.12	[X]Recurrent episodes of psychogenic depression
24112	Eu32313	[X]Single episode of psychotic depression
24171	E113400	Recurrent major depressive episodes, severe, with psychosis
43324	E112500	Single major depressive episode, partial or unspec remission
18510	Eu32.12	[X]Single episode of psychogenic depression
23731	Eu33311	[X]Endogenous depression with psychotic symptoms
28248	Eu32z13	[X]Prolonged single episode of reactive depression
16562	Eu31300	[X]Bipolar affect disorder cur epi mild or moderate depressn
11252	Eu33212	[X]Major depression, recurrent without psychotic symptoms
16861	Eu33315	[X]Recurrent severe episodes of psychotic depression
32841	8HHq.00	Referral for guided self-help for depression
35671	E113000	Recurrent major depressive episodes, unspecified
10720	Eu32y11	[X]Atypical depression
32159	E112400	Single major depressive episode, severe, with psychosis
32941	Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom
27491	E11y200	Atypical depressive disorder
57409	E112600	Single major depressive episode, in full remission
19054	Eu3y111	[X]Recurrent brief depressive episodes
24117	Eu32311	[X]Single episode of major depression and psychotic symptoms
28863	Eu32314	[X]Single episode of reactive depressive psychosis
47731	Eu33y00	[X]Other recurrent depressive disorders

36246	E290z00	Brief depressive reaction NOS
41989	Eu32211	[X]Single episode agitated depressn w'out psychotic symptoms
98252	Eu32600	[X]Major depression, moderately severe
46244	E02y300	Drug-induced depressive state
32845	Eu92000	[X]Depressive conduct disorder
37764	Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
98346	Eu32500	[X]Major depression, mild
15923	E115000	Bipolar affective disorder, currently depressed, unspecified
98414	Eu32700	[X]Major depression, severe without psychotic symptoms
31757	Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis
36616	Eu33z11	[X]Monopolar depression NOS
56609	Eu32y12	[X]Single episode of masked depression NOS
52678	Eu32312	[X]Single episode of psychogenic depressive psychosis
59386	Eu32213	[X]Single episode vital depression w'out psychotic symptoms
98417	Eu32800	[X]Major depression, severe with psychotic symptoms
73991	Eu33214	[X]Vital depression, recurrent without psychotic symptoms
46244	E02y300	Drug-induced depressive state
32841	8HHq.00	Referral for guided self-help for depression
1531	Eu31.11	[X]Manic-depressive illness
7953	Eu34100	[X]Dysthymia
11596	E11y000	Unspecified manic-depressive psychoses
12831	E115.11	Manic-depressive - now depressed
4677	E115.00	Bipolar affective disorder, currently depressed
33751	Eu31z00	[X]Bipolar affective disorder, unspecified
56273	E113500	Recurrent major depressive episodes,partial/unspec remission
60178	E11y.00	Other and unspecified manic-depressive psychoses
44674	E002.00	Senile dementia with depressive or paranoid features
23963	ZV11111	[V]Personal history of manic-depressive psychosis
27759	Eu02z16	[X] Senile dementia, depressed or paranoid type
57409	E112600	Single major depressive episode, in full remission
29451	Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms
30688	Eu3y011	[X]Mixed affective episode
22080	ZV11112	[V]Personal history of manic-depressive psychosis
28677	Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
23713	Eu31400	[X]Bipol aff disord, curr epis sev depress, no psychot symp
44693	Eu31600	[X]Bipolar affective disorder, current episode mixed
4732	Eu31500	[X]Bipolar affect dis cur epi severe depres with psyc symp
35734	E115100	Bipolar affective disorder, currently depressed, mild
20785	Eu20400	[X]Post-schizophrenic depression
37296	E115z00	Bipolar affective disorder, currently depressed, NOS
53840	Eu31y00	[X]Other bipolar affective disorders
27890	E115200	Bipolar affective disorder, currently depressed, moderate
41089	E002z00	Senile dementia with depressive or paranoid features NOS
73924	Eu31y11	[X]Bipolar II disorder
35607	E115300	Bipolar affect disord, now depressed, severe, no psychosis
63701	E115400	Bipolar affect disord, now depressed, severe with psychosis

57465	E115600	Bipolar affective disorder, now depressed, in full remission
72026	E115500	Bipolar affect disord, now depressed, part/unspec remission

Appendix 3: Read codes to identify self-harm

medcode	readterm
17378	[X]Attempted suicide
697	[X]Deliberate drug overdose / other poisoning
16907	[X]Deliberate drug poisoning
100372	[X]Fall jump/push frm high plce undt intnt occ unspecif plce
36197	[X]Falling jumping/pushed from high place undeterm intent
40284	[X]Hanging strangulation + suffocation undetermined intent
95790	[X]Int self harm by jump from high place indust/constr area
100635	[X]Int self harm by jump from high place occ oth specif plce
94377	[X]Int self harm by jump from high place occ unspecif place
73825	[X]Int self harm jump/lying bef mov obje occ oth specif plce
93837	[X]Int self harm jump/lying befr mov obje occ resid instit'n
63099	[X]Int self harm jump/lying befr mov obje occ street/highway
67586	[X]Int self harm rifl s'gun/lrg frarm disch occ resid instit
97943	[X]Int self pois org solv,halogen hydrocarb, unspec place
70391	[X]Int self poison narcotic drug other spec place
96651	[X]Int self poison nonopioid analgesic other spec place
70414	[X]Int self poison org solvent,halogen hydrocarb,in highway
96753	[X]Int self poison oth/unsp drug/medic other spec place
54695	[X]Int self poison other gas/vapour other spec place
38749	[X]Int self poison other gas/vapour school/pub admin area
94644	[X]Int self poison pesticide other spec place
96687	[X]Int self poison psychotropic drug other spec place
69343	[X]Int self poison sedative hypnotic other spec place
61546	[X]Int self poison unspecif chemical school/pub admin area
53204	[X]Int self poison/exposure to antiepileptic at home
52712	[X]Int self poison/exposure to narcotic drug at home
48934	[X]Int self poison/exposure to nonopioid analgesic at home
73776	[X]Int self poison/exposure to oth autonomic drug at home
53004	[X]Int self poison/exposure to other gas/vapour at home
35879	[X]Int self poison/exposure to other/unspec drug/medicament
96740	[X]Int self poison/exposure to pesticide at home
44508	[X]Int self poison/exposure to psychotropic drug at home
44530	[X]Int self poison/exposure to sedative hypnotic at home
51362	[X]Int self poison/exposure to unspecif chemical at home
56138	[X]Int slf hrm rifl s'gun/lrg frarm dis sch/ins/pub adm area
35868	[X]Intent self harm by crash motor vehicl occ street/highway
45166	[X]Intent self harm by crash of motor vehicl occurrn at home
94637	[X]Intent self harm by drown/submersn occ oth specif place
97794	[X]Intent self harm by drown/submersn occ unspecified place
60404	[X]Intent self harm by drowning/submersn occ resid instit'n
54091	[X]Intent self harm by hanging strangulat/suffocat occ home
30360	[X]Intent self harm by hanging strangulation / suffocation
90857	[X]Intent self harm by hangng strangul/suffoct oth spec plce
42471	[X]Intent self harm by hangng strangul/suffoct unspecif plce

64410 [X]Intent self harm by hangng strangult/suffoct resid instit
56075 [X]Intent self harm by jump from high place occ street/h'way
42097 [X]Intent self harm by jumping / lying before moving object
72734 [X]Intent self harm by jumping from high place occ at home
87882 [X]Intent self harm by oth specif means occ resid instit'n
69342 [X]Intent self harm by oth specif means occ unspecif place
45709 [X]Intent self harm by other/unspecified firearm discharge
51224 [X]Intent self harm by rifle shotgun/larger firearm disch
63100 [X]Intent self harm by smoke fire/flame occ street/highway
38008 [X]Intent self harm by smoke fire/flames occ unspecif place
67400 [X]Intent self harm by steam hot vapour/hot obj occ at home
73603 [X]Intent self harm by steam hot vapour/obj occ unspec place
97334 [X]Intent self harm by unspec mean occ sch/ins/pub adm area
61177 [X]Intent self harm by unspecif means occ at unspecif place
96224 [X]Intent self harm by unspecif means occ oth specif place
101971 [X]Intent self harm crash motor vehic occ indust/constr area
95794 [X]Intent self harm oth/unspecif firearm disch occ at home
72792 [X]Intent self pois hallucinogen in street/highway
101481 [X]Intent self pois nonopioid analgesic in street/highway
96728 [X]Intent self pois nonopioid analgesic trade/service area
58594 [X]Intent self pois organ solvent,halogen hydrocarb, home
96729 [X]Intent self pois oth/unsp drug/medic in street/highway
96714 [X]Intent self pois sedative hypnotic in street/highway
66117 [X]Intent self poison antiepileptic unspecif place
68788 [X]Intent self poison narcotic drug unspecif place
96730 [X]Intent self poison nonopioid analgesic at res institut
20650 [X]Intent self poison nonopioid analgesic unspecif place
66634 [X]Intent self poison oth autonomic drug unspecif place
68102 [X]Intent self poison oth/unsp drug/medic unspecif place
64364 [X]Intent self poison other gas/vapour unspecif place
99011 [X]Intent self poison psychotropic drug at res institut
66118 [X]Intent self poison psychotropic drug unspecif place
68790 [X]Intent self poison sedative hypnotic unspecif place
42086 [X]Intent self poison unspecif chemical unspecif place
65955 [X]Intent self poison/exposure to antiepileptic
94662 [X]Intent self poison/exposure to hallucinogen
21211 [X]Intent self poison/exposure to nonopioid analgesic
68793 [X]Intent self poison/exposure to oth autonomic drug
51309 [X]Intent self poison/exposure to other gas/vapour
68806 [X]Intent self poison/exposure to pesticide
36398 [X]Intent self poison/exposure to psychotropic drug
51292 [X]Intent self poison/exposure to sedative hypnotic
57079 [X]Intent self poison/exposure to unspecif chemical
72747 [X]Intention self harm by smoke fire/flames occurrn at home
56380 [X]Intentional self harm by crashing of motor vehicle
41400 [X]Intentional self harm by drowning and submersion

73666 [X]Intentional self harm by explosive material
46747 [X]Intentional self harm by jumping from a high place
38760 [X]Intentional self harm by other specified means
24461 [X]Intentional self harm by smoke, fire and flames
56378 [X]Intentional self harm by steam hot vapours / hot objects
42103 [X]Intentional self harm by unspecif means occurrn at home
34156 [X]Intentional self harm by unspecified means
42418 [X]Intentional self poison organ solvent,halogen hydrocarb
27713 [X]Intentional self poisoning/exposure to noxious substances
17046 [X]Intentional self-harm
67409 [X]Intentionl self harm by oth specif means occurrn at home
28531 [X]Other+unspecified firearm discharge undetermined intent
34703 [X]Overdose - amitriptyline
94725 [X]Overdose - amobarbital
46280 [X]Overdose - antidepressant
29861 [X]Overdose - aspirin
49552 [X]Overdose - barbiturate
48324 [X]Overdose - benzodiazepine
45748 [X]Overdose - diazepam
44886 [X]Overdose - ibuprofen
52931 [X]Overdose - nitrazepam
18379 [X]Overdose - paracetamol
55395 [X]Overdose - sleeping tabs
60559 [X]Overdose - SSRI
51381 [X]Overdose - temazepam
8229 [X]Para-suicide
54950 [X]Rifle shotgun+larger firearm discharge undetermin intent
24463 [X]Self carbon monoxide poisoning
24086 [X]Self poisoning from glue solvent
67956 [X]Self poisoning with paraquat
89429 [X]Self poisoning with weedkiller
45796 [X]Sequel intentn self-harm assault+event of undeterm intent
69263 [X]Sequelae of intentional self-harm
3985 [X]Suicide
3246 Attempted suicide
6595 Cause of overdose - deliberate
10057 Deliberate self-harm
46154 Drowning self
713 Drug and medicament poisoning NOS
28694 Hanging self
11753 Intent of deliberate self harm with detailed plans
58901 Jumping from bridge
44965 Jumping from building
95712 Jumping from cliff
41384 Jumping from height
89371 Jumping under train

42464	Late effects of selfinflicted injury
11708	Overdose of biological substance
3406	Para-suicide
10644	Poisoning - self-inflicted
56681	Self-asphyxiation
50482	Self-electrocution
10464	Self-harm
62382	Self-incineration
30370	Self-strangulation
89578	Self-suffocation
64227	Setting fire to self
69145	Setting self alight
54929	Shooting self
60767	Suicide + selfinflicted inj by hang/strangle/suffocate NOS
5616	Suicide + selfinflicted inj oth mean hang/strangle/suffocate
23080	Suicide + selfinflicted injury by hang/strangulate/suffocate
51685	Suicide + selfinflicted injury by suffocation by plastic bag
70946	Suicide + selfinflicted injury-jump/lie before moving object
59405	Suicide + selfinflicted injury-jumping before moving object
52458	Suicide + selfinflicted poisoning by agricultural chemical
14853	Suicide + selfinflicted poisoning by analgesic/antipyretic
16485	Suicide + selfinflicted poisoning by barbiturates
28080	Suicide + selfinflicted poisoning by corrosive/caustic subst
94412	Suicide + selfinflicted poisoning by domestic gases NOS
94412	Suicide + selfinflicted poisoning by domestic gases NOS
2557	Suicide + selfinflicted poisoning by drug or medicine NOS
69969	Suicide + selfinflicted poisoning by gas via pipeline
73628	Suicide + selfinflicted poisoning by gases and vapours NOS
70405	Suicide + selfinflicted poisoning by gases in domestic use
71375	Suicide + selfinflicted poisoning by liquified petrol gas
48871	Suicide + selfinflicted poisoning by motor veh exhaust gas
33596	Suicide + selfinflicted poisoning by oth sedatives/hypnotics
22199	Suicide + selfinflicted poisoning by other drugs/medicines
61618	Suicide + selfinflicted poisoning by other gases and vapours
66621	Suicide + selfinflicted poisoning by solid/liquid subst NOS
30292	Suicide + selfinflicted poisoning by solid/liquid substances
27522	Suicide + selfinflicted poisoning tranquilliser/psychotropic
21027	Suicide and self harm
66109	Suicide and self inflicted injury by Amylobarbitone
99566	Suicide and self inflicted injury by Barbitone
94442	Suicide and self inflicted injury by Phenobarbitone
21029	Suicide and selfinflicted injury
46456	Suicide and selfinflicted injury by burns or fire
64744	Suicide and selfinflicted injury by crashing motor vehicle
101906	Suicide and selfinflicted injury by crashing of aircraft
15177	Suicide and selfinflicted injury by cutting

36255	Suicide and selfinflicted injury by cutting and stabbing
65448	Suicide and selfinflicted injury by cutting and stabbing NOS
31854	Suicide and selfinflicted injury by drowning
71159	Suicide and selfinflicted injury by electrocution
98594	Suicide and selfinflicted injury by extremes of cold
66915	Suicide and selfinflicted injury by firearms and explosives
101056	Suicide and selfinflicted injury by firearms/explosives NOS
13557	Suicide and selfinflicted injury by hanging
56137	Suicide and selfinflicted injury by hunting rifle
23753	Suicide and selfinflicted injury by jumping from high place
65309	Suicide and selfinflicted injury by other firearm
47501	Suicide and selfinflicted injury by other means
71843	Suicide and selfinflicted injury by other means NOS
66063	Suicide and selfinflicted injury by other specified means
36084	Suicide and selfinflicted injury by scald
28115	Suicide and selfinflicted injury by shotgun
27470	Suicide and selfinflicted injury by stabbing
96430	Suicide and selfinflicted injury caustic subst, excl poison
41241	Suicide and selfinflicted injury NOS
51328	Suicide and selfinflicted poisoning by other carbon monoxide
49135	Suicide and selfinflicted poisoning by other utility gas
58605	Suicide+selfinflicted injury-jump from high place NOS
61113	Suicide+selfinflicted injury-jump from natural sites
42937	Suicide+selfinflicted injury-jump from oth manmade structure
61569	Suicide+selfinflicted injury-jump from residential premises
99427	Throwing self in front of train
92308	Throwing self in front of vehicle
171	Overdose of drug